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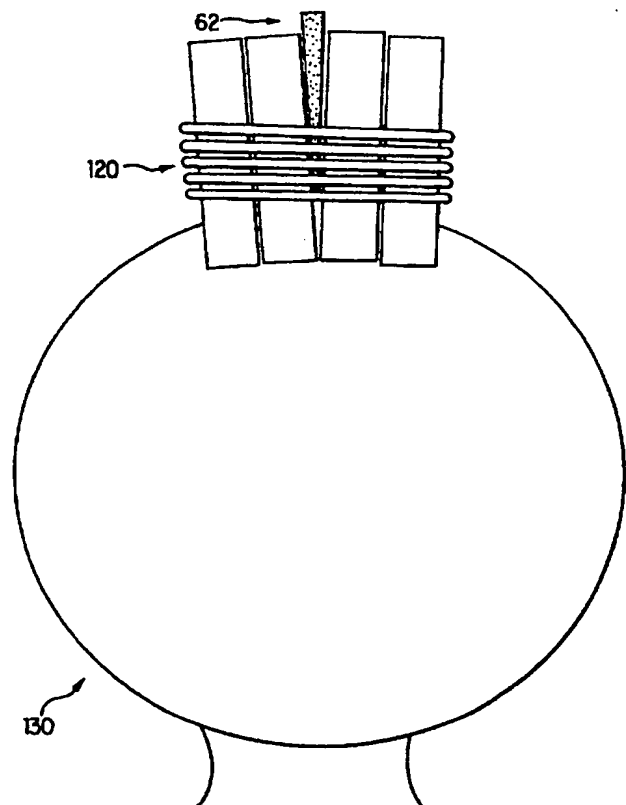
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(54) Title: TRANSCRANIAL BRAIN STIMULATION

## (57) Abstract

An apparatus and method for transcranial magnetic brain stimulation. The apparatus allows transcranial stimulation at higher power efficiency and lower heat generation than prior available magnetic stimulator coils without an iron core. Use of the apparatus allows an improved method for active localization of language function. The device can also be used in rapid rate transcranial magnetic stimulation for the treatment of depression.



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## TRANSCRANIAL BRAIN STIMULATION

### **Related Applications**

This application claims the priority of U.S. Provisional Application Serial No. 60/023,421, filed August 15, 1996 (pending), and of U.S. Patent Application Serial No. 08/345,572, filed November 28, 1994 (pending), the disclosures of which are incorporated herein by reference.

### **Field of the Invention**

The present invention relates to an apparatus for transcranial magnetic brain stimulation. The invention also relates to methods for localizing and characterizing speech arrest, and for treatment of depression using transcranial magnetic stimulation.

### **Background of the Invention**

#### **The Magnetic Stimulator Apparatus**

Magnetic stimulation of neurons has been heavily investigated over the last decade. Almost all magnetic stimulation work has been done *in vivo*. The bulk of the magnetic stimulation work has been in the area of brain stimulation.

Cohen has been a rather large contributor to this field of research (See e.g., T. Kujirai, M. Sato, J. Rothwell, and L. G. Cohen, "The Effects of Transcranial Magnetic Stimulation on Median Nerve Somatosensory Evoked Potentials", *Journal of Clinical Neurophysiology and Electroencephalography*, Vol. 89, No. 4, 1993, pps. 227 - 234, the disclosure of which is fully incorporated herein by reference.) This work has been accompanied by various other research efforts including that of Davey, et al. and that of Epstein (See, K. R. Davey, C. H. Cheng, C. M. Epstein "An Alloy - Core Electromagnet for Transcranial Brain Stimulation", *Journal of Clinical Neurophysiology*, Volume 6, Number 4, 1989; and, Charles Epstein, Daniel Schwartzberg, Kent Davey, and David Sudderth, "Localizing the Site of Magnetic Brain Stimulation in Humans", *Neurology*, Volume 40, April 1990, pps. 666-670, the disclosures of which are fully incorporated herein by reference).

Generally, the magnetic stimulation research has used air type coils in their stimulators. These coils are so named due to the fact that they lack a magnetic core. A well known producer of such coils is Cadwell, which produces a variety of different models. One of the goals of the present inventors has been to provide magnetic stimulator devices for use in a variety of applications, which are improvements over the devices previously used in the art. In our prior pending patent application, U.S. Patent Application Serial No. 08/345,572, filed November 28, 1994, which is the parent to the present application (the disclosure of which is fully incorporated herein by reference), a variety of such devices were disclosed for the use in peripheral nerve stimulation. Accordingly, it is an object of the present inventors herein to provide further devices for use in central nervous system stimulation in general, and transcranial brain stimulation in particular.

### The Treatment of Depression

Transcranial magnetic stimulation is known to non-invasively alter the function of the cerebral cortex. (See e.g., George MS, Wassermann EM, Post RM, Transcranial magnetic stimulation: A neuropsychiatric tool for the 21st century, *J. Neuropsychiatry*, 1996; 8: 373-382, the disclosure of which is fully incorporated herein by reference). The magnetic fields used are generally generated by large, rapidly-changing currents passing through a wire coil on the scalp. Two recent studies have suggested that rapid rate transcranial magnetic stimulation (rTMS) may be used for exploring the functional neuroanatomy of emotions: healthy volunteers who received left pre-frontal stimulation reported an increase in self-rated sadness, while, in contrast, right pre-frontal stimulation caused an increase in happiness. (See, Pascual-Leone A., Catala MD, Pascual AP, Lateralized effect of rapid rate transcranial magnetic stimulation of the prefrontal cortex on mood, *Neurology*, 1996; 46: 499-502; and, George MS, Wasserman EM, Williams W., et al., Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation of the prefrontal cortex, *J. Neuropsychiatry Clin. Neurosci.* 1996; 8: 172-180, the disclosures of which are fully incorporated herein by reference.)

Other reports have begun to delineate the therapeutic use of rTMS in depression. The earliest such studies used round, non-focal coils centered at the cranial vertex, with stimulation rates well under 1 Hertz (Hz). Results were promising but not always statistically significant. (See, Hoflich G., Kasper S. Hufnagel A. et al., Application of transcranial magnetic stimulation in treatment of drug-resistant major depression: a report of two cases, *Human Psychopharmacology*, 1993; 8: 361-365; Grisaru N., Yaroslavsky U., Abarbanel J., et al., Transcranial magnetic stimulation in depression and schizophrenia, *Eur. Neuropsychopharmacol.* 1994; 4: 287-288; and, Kilbinger HM, Hoflich G., Hufnagel A., et al., Transcranial

magnetic stimulation (TMS) in the treatment of major depression: A pilot study, *Human Psychopharmacology*, 1995; 10: 305-310, the disclosures of which are fully incorporated herein by reference.)

Subsequently, George et al., described striking improvement in some depressed patients from treatment with rTMS over the left pre-frontal cortex. (See, George MS, Wasserman EM, Williams WA, et al., Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression, *NeuroReport*, 1995; 6: 1853-1856; and, George MS, Wasserman EM, Williams WE, Kimbrell TA, Little JT, Hallett M., Post RM, Daily left prefrontal rTMS improves mood in outpatient depression: a double blind placebo-controlled crossover trial, *Am. J. Psychiatry*, 1997 (in press), the disclosures of which are fully incorporated herein by reference). The largest such study to date was reported by Pascual-Leone et al., who used a five-month double blind placebo-controlled cross over design with five different treatment conditions. (See, Pascual-Leone A., Rubio B., Pallardo F. Catala MD, Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression, *The Lancet*, 1996; 348: 233-237, the disclosure of which is fully incorporated herein by reference.) Left pre-frontal rTMS was uniquely effective in 11 of 17 young (less than 60 years of age) psychotically depressed and medication resistant patients.

Accordingly, further to the work which has been done thus far in this field, it is also a goal of the present inventors to provide improved apparatus and methods for transcranial magnetic stimulation, and for the treatment of depression using such stimulation, as described more fully hereafter.

#### The Localization of Speech Arrest

With respect to the methods previously used for the localization of speech arrest, active localization of language function has traditionally been possible only with invasive procedures. The dominant hemisphere can be determined using the intracarotid amobarbital or Wada test. Cortical areas critical to language can be mapped using electrocorticography in the operating room, (See e.g. Penfield, 1950, cited below) or extra-operatively through electrode grids implanted in the subdural space. (See e.g. Lesser, 1987, cited below). The Wada test and electrocorticography have contributed greatly to our current understanding of language organization. However, because of their complexity and potential morbidity, these techniques are confined almost entirely to patients undergoing surgery for intractable epilepsy.

In the past decade, positron emission tomography and functional magnetic resonance imaging have shown promising results for language localization. But these newer imaging technologies require complex and expensive equipment, and have other limitations in the form of poor temporal resolution or a restricted test environment. The correlation between the degree of metabolic change in different brain areas and their importance for a given cognitive task remains unknown. (See e.g., Ojemann, cited below).

At least four groups have reported lateralized speech arrest using rapid-rate transcranial magnetic brain stimulation (rTMS) in epilepsy patients. (See e.g., Pascual-Leone, 1991, Michelucci, 1994, Jennum, 1994, and Epstein, 1996, cited below). The results showed a high correlation with the Wada test, but sensitivity in the two largest series was only 50-67% (See, e.g., Jennum, 1994, and Michelucci, 1994, cited below). Most of these studies used large circular magnetic coils, along with stimulus parameters that may carry a risk of inducing seizures. (See, e.g. Pascual-

Leone, 1993, cited below). Thus, the initial rTMS techniques were not optimal for detailed localization or for studies involving normal subjects.

Consequently, further to the work which has previously been done, it is also a goal of the present inventors to provide improved apparatus and methods for localization and characterization of brain function. As described hereafter, we recently described modifications of rTMS that produce lateralized speech arrest with reduced discomfort, a repetition rate as low as four Hertz, and a combination of stimulus parameters that comply with recent recommendations for safety in rTMS (See also, Epstein CM, Lah JJ, Meador K, Weissman JD, Gaitain LE, Dihenia B, Optimum stimulus parameters for lateralized suppression of speech with magnetic brain stimulation, *Neurology*, 47: 1590-1593 (December 1996), the disclosure of which is fully incorporated herein by reference). The technique is useful for detailed studies of magnetic speech arrest in normal individuals.

#### **Summary of the Invention**

An object of the present invention is to provide an improved apparatus for transcranial magnetic brain stimulation.

A further object of the present invention is to provide an improved method for characterizing and localizing brain function.

A further object of the present invention is to provide an improved method for characterizing and localizing speech arrest.

A further object of the present invention is to provide an improved method for treatment of depression.

As disclosed more fully hereafter, an apparatus is described for use in transcranial brain stimulation. The apparatus is designed to produce a focussed magnetic field which can be directed at sites on the brain of interest or importance. The device consists of at least one, but preferably four magnetic cores. The cores are preferably constructed of a



ferromagnetic material. The cores can have an outer diameter between approximately 2 and 7 inches, and an inner diameter between approximately 0.2 and 1.5 inches. The material of the cores has a magnetic saturation of at least 0.5 Tesla, and preferably at least 1.5 Tesla, or even 2.0 Tesla or higher. In the preferred embodiment, the core conforms in construction to the shape of the head to improve its efficacy. A visualization and location port is included to assist with the precision placement of the core on the head, and to assist with exact marking of the stimulator's position.

Using the described apparatus and method, an optimized technique for transcranial magnetic brain stimulation is provided which has a variety of useful applications. For example, the present apparatus and method can be employed for brain stimulation in a therapeutic protocol for the treatment of depression. In addition, the apparatus and method can be used for the localization and characterization of brain function. For example, detailed anatomic localization of speech arrest and effects on other language function can be studied. The invention therefore provides devices and methods for non-invasive stimulation and treatment of the brain, and for studying and characterizing brain function, which are improvements over the procedures of the prior art.

Using the apparatus and technique on four normal righthanded volunteers, to study speech arrest for example, it was determined that all were dominant for magnetic speech arrest over the left hemisphere. While subjects counted aloud, points of speech arrest were mapped on a one-centimeter grid over the left frontal region. Compound motor action potentials from muscles in the right face and hand were mapped onto the same grid. Subjects were then tested in reading, writing, comprehension, repetition, naming, spontaneous singing, and oral praxis during magnetic

stimulation. Finally, mean positions for speech arrest and muscle activation were identified on three dimensional MRI.

All of the subjects tested using the present technique had complete, lateralized arrest of counting and reading with magnet stimulation over the left posterior-inferior frontal region. Writing with the dominant hand, comprehension, repetition, visual confrontation naming, oral praxis, and singing were relatively or entirely spared, with rare aphasic errors. In two subjects, melody was abolished from singing during stimulation over the right hemisphere. In all four subjects, the region of speech arrest was highly congruous with the region where stimulation produced movement of the right face, and overlay the caudal portion of the precentral gyrus. This constellation of behavioral and anatomic findings is similar to that found in aphemia, and supports a modular theory of language organization in the left hemisphere.

In patients with refractory depression, the stimulator of the present invention was used to stimulate the brain with magnetic pulses using rapid rate transcranial magnetic stimulation over the left prefrontal region of the brain. In a group of 32 patients aged 22-64, all Hamilton Depression (Ham-D) scores were above 20 prior to treatment. Twenty-eight (28) patients completed treatment: average Ham-D scores fell from thirty one (31) to fifteen (15), and individual scores fell to less than ten (10) in fourteen (14) out of twenty-eight (28) of the subjects. Sixteen (16) out of the twenty eight (28) patients were clear responders to rTMS. Two enrollees dropped out because of pain during stimulation, and three had possible adverse effects during the course of treatment that we were unable to connect causally with rTMS. Thus, it was found that rTMS could be used as a simple and effective treatment for many patients with refractory depression who would otherwise be candidates for ECT.

**Brief Description of the Drawings**

Figure 1 is a top view of a transcranial magnetic brain stimulator in accordance with the present invention while Figure 1A is a side view thereof..

Figure 2 is a top view of a second embodiment of a transcranial magnetic brain stimulator in accordance with the present invention with Figure 2A being a side view thereof.

Figure 3 is a front view of a transcranial magnetic brain stimulator formed from 4 cores in accordance with Figures 1 or 2, as positioned on a schematic human head.

Figure 4 is a side view of the stimulator of Figure 3 on a schematic human head.

Figure 5 presents a series of three tables showing experimental results from the use of the present stimulators for the treatment of depression. Table 1 shows the antidepressant dosages of indicated medication received by experimental subjects prior to rTMS. Table 2 shows the ages and sex of the responders and non-responders to treatment. Table 3 shows the diagnoses of the responders and non-responders to treatment.

Figure 6 is a histogram of the differences between post-treatment and pre-treatment Hamilton Depression scores for all patients completing a course of rTMS.

Figure 7 is a graph showing comparative results for use of the present stimulator in comparison to several other devices.

Figure 8 shows the components used to form a third embodiment of a transcranial magnetic brain stimulator in accordance with the present invention.

**Detailed Description of the Invention and the Preferred Embodiments**

### The Magnetic Brain Stimulator

To accomplish the magnetic stimulation described in the present application, an improved apparatus for transcranial magnetic brain stimulation is disclosed herein, as further set forth below and in the accompanying drawings. The design of the apparatus is related to the designs previously described in U.S. Patent Application Serial No. 08/345,572 filed November 28, 1994 (pending), the disclosure of which is fully incorporated herein by reference, and upon which the present application claims priority. Diagrams of the novel magnetic stimulator are provided in Figure 1-3. The specifications and details of the components of the stimulator are shown therein. The devices of the present invention induce electric fields similar in distribution to those from a Cadwell water-cooled figure-eight coil. However, the present inventions are much smaller, quieter, and more efficient, requiring no special cooling.

As shown in Figures 1 and 2, a core for a magnetic nerve stimulator is provided for stimulation of the brain. The stimulator core 27 is made of a magnetic material, preferably a ferromagnetic material. In the preferred embodiments, the material of the core has a magnetic saturability of at least 0.5 Tesla. Higher saturabilities are preferred, however, with saturabilities of at least 1.5 Tesla or higher, or even 2.0 Tesla or higher recommended in the preferred embodiments. Preferred materials for the core include vanadium permendur or 3% grain oriented steel.

As shown in Figure 1, in the preferred embodiment, core 27 is cut from an oval winding of 2 mil vanadium permendur. Two cores can, in fact, be cut from a single oval winding, by cutting one core from each side of the oval. For illustration purposes, only a single core is shown in the diagram of Figure 1.

The method of construction of such a core is as described previously in our patent application, which is the parent to the present application,

U.S. Application Serial No. 08/345,572, filed November 28, 1994. The best cores are constructed from thin laminate, highly saturable material (i.e. materials with a saturability of at least 1.5 - 2.0 Tesla, although less saturable materials with a saturability of 0.5 Tesla and higher can be used as well).

A typical core can be wound using two mil stock of vanadium permendur. A long ribbon of such material is wound on a mandrel (e.g. a mandrel of wood or plastic) for the radius, thickness and depth desired. Each side of the ribbon is coated with a thin insulative coating to electrically isolate it from its neighbor. After cutting the core from the entire oval winding, a suitable core might span an angle of approximately 208°, or in the range of about 205-215°, as shown in Figures 1, 2 and 8. Other angles are possible, as well, however, though not preferred, as described below.

Once the ribbon has been wound on the mandrel to the desired dimensions, it is dipped in epoxy to freeze its position. Once the epoxy has dried, the mandrel is removed and the core may be cut for the span of angle desired. The cut may destroy the electrical isolation of adjacent laminations. Each cut must be finely ground so that it is smooth, and then a deep etch performed. The deep etch is performed by dipping each of the cut ends in an acid bath. This causes the cut ends to delaminate slightly, but maintains the electrical isolation of the laminations. Failure to perform this deep etch seems to result in considerable eddy current loss and heating at the cut ends of the core. Following the deep etch, the ends are brushed with epoxy to maintain the shape and structural integrity of the core. The final step of the construction is to wind a coil of insulated wire about the core. A typical inductance for a core of this type is about 20 $\mu$ H. The present invention, however, may be practiced at other inductances or magnetic field strengths, if desired.

As an alternative to cutting the core as one entire section, the core can be cut as a semi-circular section. In this method of manufacture, the small triangular sections 34 at the bottom of the core are then cut separately, and attached to the semi-circular section as shown in the Figures. Preferably, the smaller triangles are also made from vanadium permendur. If necessary, however, the triangles can be any material or alloy that has a saturation of at least 0.5 Tesla, and which can be worked by one of ordinary skill in the art. A suitable alloy for the triangular sections, for example, is 2 mil 50% nickel alloy.

As shown in Figure 1, in the preferred embodiment, core 27 has an outer diameter of approximately 4.75 inches. The core 27 has an inner semi-circular aperture 38 at the center of the core 27. Inner semicircle 38 has a diameter of approximately 0.75 inches. In a version where the smaller triangles are separate, triangular sections or wedges 34 are attached to the larger semi-circular section. Triangular sections 34 have a length on longer side 40, in contact with semi-circular section 30, of approximately 1.375 inches, and a length of approximately 0.75 inches on shorter side 42 which is approximately coplanar with the outside of semi-circular section 30. As shown in Figure 1A, the cross sectional width of core 27 is approximately 0.625 inches.

A second version of the core is shown in Figure 2. Core 51 is merely a smaller version of the core 27 shown in Figure 1. Core 51 has a outer diameter of 3.75 inches, and an inner diameter 56 of approximately 0.875 inches. The triangular sections 54 attached to the ends of the semi-circular core have a length of approximately 0.47 inches on shorter side A, and a length of approximately 0.875 inches on longer side B. As mentioned with respect to Figure 1, the cores are preferably cut such that the triangular sections 54 are an integral part of the core 51, however, the triangular sections 54 can be cut separately and attached to a semi-circular

section of core, if necessary or desired. In the preferred embodiment, the core with triangular sections subtends an angle of approximately 208 or 205-215 degrees as measured from the center of inner diameter 56 to the far edge of shorter side A. This embodiment shows the core as having a thickness of about 0.5" (Figure 2A).

A third embodiment of the core is shown in Figure 8. In this embodiment, two separate layers of materials are used. An inner layer 74 is provided which is constructed of 2 mil vanadium permendur. Outer layer 79 is constructed of 2 mil 50% nickel alloy. The dimensions of the respective layers are shown on the Figure. The inner and outer ovals are wound and separately cut. A single oval can be used to cut two inner cores, and a second oval can be used to cut two outer cores. The inner layer 74 and the outer layer 79 are then nested together as shown in Figure 8.

As shown in the Figures, each of the cores of the stimulator is preferably an open core, i.e. the core forms an open arc, and does not constitute a closed toroid. An approximately C-shaped core is preferable. In accordance with the present design, at least a portion of the core of the stimulator conforms, at least approximately, to the shape of the head. In the preferred embodiment, a hemispherical stimulator, having at least one, but preferably four adjacent, cores (see Figure 3) made of saturable or highly saturable ferromagnetic material, is used, as shown in the Figures.

The span of the core affects both the penetration depth of the magnetic field and the magnitude of the field. While a variety of angles are acceptable for the curvature of the arc of the core, a core of 208 degrees or approximately in the range of about 205 - 215 degrees is shown in the Figures for preferred embodiments. In other embodiments, cores of approximately 190 - 230 degrees can be utilized. Alternatively, a core

spanning an arc of approximately 180 - 270 degrees is also possible, although not necessarily as effective.

In the preferred embodiment, to form the stimulator, four cores are positioned approximately side by side to form a complete magnetic stimulator. Although more than four cores or less than four cores are possible, four are preferred. As shown in Figures 3 and 4, two pairs of cores are placed side by side to form a hemisphere designed for placement on the head. The combined cores are wound with a series of windings of wire. In the preferred embodiment, approximately nine to ten turns of wire are used; approximately nine (9) turns of wire being preferably wound around the larger stimulator formed of cores of Figure 1, and approximately ten (10) turns of wire being wound around the smaller stimulator formed of cores of Figure 2. As shown in Figures 3 and 4, approximately four - five (4-5) turns of wires are wound around each half of the stimulator, i.e., approximately four to five turns are wound around a first side of the stimulator, and another four to five turns are wound around the second side of the stimulator.

In accordance with the present invention, it is also preferred that the stimulator be provided with a visualization and location port for viewing and marking the head and locating the stimulator thereon. In the present invention, a space is left open between the two pairs of cores to form a center port 62 (see Figure 3). Center port 62 extends from the top of the stimulator down to the surface of the patient's head as shown in Figure 3. It is preferred that a length of plastic or copper tubing be inserted in this area to form the port. Port 62 is of sufficiently large diameter that a marking device such as a pen or felt marker can be inserted into the port 62 through the stimulator to mark the head's surface (or to mark a cap worn on the head). Thus, as an illustration of the construction of the port 62, the internal ink containing cylinder can be removed from a standard



writing device, such as a Papermate™ pen, leaving the pen's outer plastic section of tubing empty. This outer plastic section of tubing can be inserted between the two pairs of cores to serve as the tubing for the port. The internal, ink containing portion of the pen can later be inserted down and through this port to mark the patient's head. Any suitable tubing and any marker of smaller diameter than the tubing, can of course, be used, and the present example is not meant as a limitation.

Port 62 has importance both as a means to precisely mark where a stimulator is located on the head, and as a means to precisely position the stimulator. When the stimulator is placed on the head, the marking device or pen can be inserted down the port and through the stimulator to make a mark on the head of the patient. The mark serves as an effective reference, indicating exactly where the stimulator was positioned. This provides a convenient and effective means of precisely recording the stimulator location for later reference.

Likewise, if it is desired that the stimulator be centered over a particular region of the head a mark can first be placed on the head in the appropriate area. Or, if it is desired that the stimulator be placed on the same location in successive sessions, an appropriate mark can be left on the head after the first positioning. In either situation, by viewing down the port of the stimulator, the stimulator can be moved around over the head until the marked area is within view through the port, so that the stimulator can be positioned on the exact location desired.

Figure 7 shows a comparison of several coils at 30% output, measured in air. At the critical depth of two cm below the coil, the present ferromagnetic core system, as disclosed herein, induces approximately twice the electric field of an oversized plain coil, and more than twice that of a standard commercial coil from Cadwell. The power improvement is the square of this ratio.

Thus, in the present design, the semi-circular configuration optimally combines with a double-loop wire coil, and the concave active surface delivers maximal magnetic flux to the brain and other physiological targets. Of the large number of other magnetic stimulators that have been developed or are in use, the present inventors are not aware of any other design having comparable advantages or performance. In the present device, focal magnetic stimulation is provided with an approximate twofold amp-turn efficiency and 1/4th the heat generation of prior available stimulation coils without a ferromagnetic core. Triangular extensions and curvature of the active surface significantly improve efficiency of brain stimulation. The device allows more powerful and focused stimulation than any existing alternative, and, alternatively, allows conventional stimulation at a much lower energy cost. It uniquely allows continuous high speed magnetic stimulation without requiring special provisions for cooling. Moreover, projection of the magnetic field into the brain is effective even when the core is partially saturated.

In the preferred embodiment of the present invention, the electrical circuitry and parameter referred to in co-pending application Serial No. 08/345,572 filed November 28, 1994 are employed with the stimulator taught herein. Alternatively, any other suitable circuit and power source can be used, as well be apparent to those of ordinary skills in the art.

#### Magnetic Brain Stimulation for Localization of Language Function

Among the many suitable applications of this device, the present inventions may be used to provide an improved technique for active localization and characterization of brain function. In one particular embodiment, it is possible to locate and characterize language function. This technique was tested on four subjects, all being right-handed male physicians, ages 31-49, studied under informed consent. All had previously

shown dominance for magnetic speech arrest over the left hemisphere. (See, e.g., Epstein, 1996, cited below)

For magnetic mapping, the subjects were seated comfortably and unrestrained. The head was covered with a thin latex swim cap, which simplified position measurements over a large scalp area that included up to 100 possible sites of stimulation. Any redundant latex folds were taped down, and the position of the cap was labeled using as landmarks theinion, distance from nasion, earlobes, and vertex. One-centimeter grid lines were drawn over the posterior frontal region and labelled alpha-numerically. Relaxed motor threshold was determined as previously described, (See Epstein, 1996, cited below) using the dominant first dorsal interosseous (FDI) or abductor pollicis brevis (APB) to represent the hand. With this technique, threshold is defined as the lowest intensity of stimulation that produces compound motor action potentials (CMAPs) of 50  $\mu$ V or greater on five of ten trials; (See, e.g. Pascual-Leone, 1993, cited below) consequently averaged CMAPs are expected to be non-zero at threshold.

Mapping of CMAPs from FDI or APE was performed using the disclosed ferromagnetic core (vanadium permendur) stimulation coil, with the induced electric field maximum beneath the center point of the device. A small port through the middle allows precise marking and positioning. The coil was placed so that the induced electric field was aligned horizontally—that is, along a sagittal or axial plane. With the right hand relaxed, we averaged eight responses to left hemisphere stimulation at a rate of 1 Hz. Testing was extended in all directions on the grid until a 2-cm rim of absent responses completely surrounded the area of activation. Mapping was done in the same manner from the right orbicularis oris (ORO) in all subjects, but facilitation was used if no response could be obtained during relaxation at stimulator outputs up to 20% greater than hand motor threshold.

Speech interruption was tested with the same coil while the subject counted briskly and repetitively upward from one to 20. The stimulator was activated at a rate of four Hertz about the time the count reached the number "five." Stimulator output was adjusted differently in the four subjects, from a level that barely produced complete speech arrest to intensities 5—10% higher. The degree of speech interruption was rated by both subject and observers as complete, moderate, slight, or absent.

In a separate session, the stimulation coil was repositioned over the area of maximum speech arrest. After obtaining appropriate baselines, the following tasks were carried out during stimulus trains of 3-5 seconds duration:

- reading unfamiliar material aloud;
- reading silently and then describing content;
- spontaneously describing the events of the "cookie theft picture";
- hearing and obeying two-step commands with inverted syntax;
- visual confrontation naming, using slide projections of 14 familiar objects;
- writing numbers from "one" upward;
- repetition of two brief phrases, including "no ifs, ands, or buts";
- singing lyrics to a familiar song;
- tests of oral praxis, including tapping the upper teeth with the tongue, licking the lips from side-to-side, and alternating lip puckering and blowing.

Writing and visual confrontation naming were then repeated with the stimulator placed 2 cm anterior to the position of maximum speech arrest. Singing was repeated during stimulation of the homologous area

over the right hemisphere. A delay of ten seconds or more was always present between stimulus trains.

For construction of a two-dimensional map, the average CMAPs representing each muscle were scaled to a maximum of one. Complete speech arrest was arbitrarily assigned a magnitude of 1.0, moderate speech interruption 0.5, and slight speech interruption 0.25. Bubble charts were plotted with the area of each bubble corresponding to the magnitude of the response at that site. For each muscle and for speech arrest, a two dimensional mean position on the grid was calculated. These positions were marked on the swim cap, which was then replaced on the subject's head and realigned to the previous anatomic landmarks. Each center of gravity was marked with a capsule of vitamin E for identification on MRI. Cranial MRI was then performed.

Measurement of the induced electric field was performed in a spherical, saline filled model head of radius 7.5 cm, using a differential probe with silver-silver chloride electrodes as previously described. (See Epstein, 1996, cited below). This was followed by three dimensional reconstruction of the MRIs.

In this test of the invention, complete speech arrest was obtained over the left posterior-lateral frontal lobe during counting and reading aloud in all four subjects. In three subjects counting and reading were entirely normal on right-sided stimulation at the same intensity. The other subject had slight dysarthria with stimulation on the right. Remarkably, visual confrontation naming was intact for most objects in all subjects, with variable slowing of responses and slight dysarthria. Rare aphasic errors usually consisted of word substitutions. Writing numerals was intact in the right hand at both left frontal sites of simulation, even though one subject had slight jerking of the right upper extremity. The other three subjects underwent a second writing test in which they spelled out the numbers,

again with no difficulty. Singing was consistently easier than spontaneous speech, with slight to moderate slowing or dysarthria but with preservation of melody. However, in two of three subjects so tested, stimulation over the right hemisphere produced flattening and loss of melody that was apparent to both the subject and the observers. This effect was obtained in one subject at the same intensity used for speech arrest, and in the other only at a setting 10% higher.

Resting motor maps were easily constructed for the hand using FDI in three subjects and APB in one. Only two subjects had facial CMAPs obtainable from the ORO at rest. The other two maps of ORO were obtained with facilitation: one subject gently pursed his lips, while the other counted aloud during averaging of CMAPs.

In one series of tests, speech arrest was tested at a relatively low intensity, equal to 95% of resting threshold in FDI. In another series of tests, speech was tested at a higher relative intensity of 118%, and facilitation was not necessary for recording of facial CMAPs. But the use of different hand muscles and different kinds of facilitation for ORO had little effect on the relative map positions. The area of stimulation that produced speech arrest was always congruous with the area which gave motor responses from ORO. In the coronal plane, the center of gravity for SA lay an average of 0.5 cm from that for ORO. In the axial plane, the center of gravity for SA lay, on average, 0.7 cm posterior to that for ORO.

The smallest rectangle of the mapping grid that encloses the sites of speech arrest can be described as the "local area." Within the local area, the first two subjects showed no correlation between the degree of speech arrest and the magnitude of facial muscle contraction. A significant correlation was found for subjects 3 and 4, in the latter the level of stimulation was relatively high during language mapping. Thus, the

congruence for speech arrest and facial movement was not consistently present on a detailed level.

Through our studies it has therefore been found that magnetic stimulation of the dominant hemisphere produces specific impairments of language output, and not simply anarthria: some modalities of speech are affected profoundly, but others minimally or not at all. Magnetic interference most affects spontaneous speech. It has less effect on repetition, confrontation naming, and singing, while writing is entirely spared. Magnetic speech arrest is not Broca's aphasia. The site of action is congruous with the region of facial motor responses, rather than anterior to the motor strip as might be expected from classic models of language organization.

During neurosurgical mapping procedures, with direct electrical stimulation of the cortex, speech arrest can be obtained over extensive areas of both hemispheres. The most frequent site is the facial portion of the primary motor area, near the junction of the Sylvian and Rolandic fissures. (See, e.g. Penfield, 1950 and Ojemann, cited below) This is the same region implicated in magnetic speech arrest over the dominant hemisphere. In contrast with electrocorticography, however, magnetic stimulation produces speech arrest in only one location, and has little effect on confrontation naming in this area or anterior to it.

Many features of magnetic speech arrest are similar to those of the articulatory disorders variously described as pure motor aphasia, pure anarthria, cortical dysarthria, simple aphasia, phonetic disintegration, and aphemia. Such cases have been described with subcortical lesions of the lateral frontal region, but when cortical lesions are responsible they are found in the lower motor strip and Rolandic operculum. Clinical findings include marked slowing of speech output, stuttering, preservation of grammar, and relative preservation of repetition and singing. Writing is

generally spared. Many authors, including Pierre Marie, distinguish a pure articulatory disturbance from aphasia on the bases of intact comprehension, reading, and writing. (See, e.g. Marie and Schiff, cited below) Others have noted the frequent association with lexical errors (Kaminski) and other forms of language disorganization, and prefer to classify aphemia as a limited form of aphasia (L&L).

The function most impaired by magnetic stimulation is the *de novo* assembly of spontaneous speech and the complete arrest of language output by stimulation rates as low as two per second is a striking feature. The rapid, precise, coordinated synthesis of multiple lingual-buccal-vocal movements into consecutive phonemes represents one of the most extraordinary tasks carried out by the human motor system, and it's reasonable to hypothesize that a specialized language module may be dedicated to it. Such a module would be tightly interwoven with the primary motor cortex; as a final common pathway it might be more difficult to bypass with parallel pathways of language processing. Magnetic interference with speech may be lessened when the construction of phonemes is cued by speech reception, melody, or the presentation of familiar visual objects. This amelioration of the deficit by other neural inputs stands in distinction to aphemia and also to the classical aphasias, all of which are characterized by impairment of repetition.

Functional maps of the type used here have important limitations, including the relatively large area and elliptical shape of the induced electric field. This shape produces a well-known distortion of the magnetic map, in which sites of excitation are "smeared" more extensively in the direction of the electric field. Assuming that spatial smearing is symmetrical, however, the scalp center of gravity as calculated here will be unaffected, and should accurately reflect the mean position of excitation even in the absence of formal deconvolution.



In comparison to electrocorticography, magnetic mapping of the cerebral cortex has important advantages that go beyond its relative safety and ease of uses. One of these, obviously, is the ability to study both hemispheres of the normal brain. Another is the robustness of motor effects. Direct electrical stimulation of the cortex in conscious subjects fails to activate any hand movement in as many as 35%, fails to produce movement of the face or tongue in up to 83%, and occasionally fails to identify areas of speech arrest anywhere in the dominant hemisphere. Thus it is often impossible, using electrocorticography, to make a clear physiological distinction between different cortical regions; there simply are not enough sites of activation in a given subject. But with appropriate techniques magnetic stimulation will *always* activate movement of multiple hand muscles in normal subjects, and has produced speech arrest in all but one of several dozen normal subjects we have surveyed thus far. The reason for this surprising advantage of transcranial magnetic stimulation is unknown, but may relate to a consistent electric field vector over a larger volume of cortex.

Our technique has not yet been validated against the Wada test, and thus cannot necessarily substitute for it at present. However, the usual Wada test patient who harbors intractable epilepsy and a high incidence of structural lesions may have atypical patterns of language organization. The Wada procedure is also complicated by a limited time frame and unpredictable drug effects, so that its results may not extrapolate to the normal population.

Analysis of magnetic speech arrest supports the current interpretation of language organization as modular, rather than the older concept of a single output area that controls multiple functions. The robustness and convenience of magnetic mapping should further facilitate

the investigation of language function in normal brains, and improve our understanding of recovery in those that have suffered impairment.

#### Magnetic Brain Stimulation for Treatment of Depression

In accordance with the present invention, the present apparatus can also be used for the treatment of depression. It has been found that magnetic transcranial brain stimulation can be an effective treatment in a variety of patients, including those who are psychotically depressed or medication resistant. Treatment of refractory depression using the present device having a core of a magnetic or preferably ferromagnetic material is believed to be more effective than use of the devices previously disclosed in the art. Although the use of left prefrontal rTMS is preferred based on current understanding, it may be possible that other forms of stimulation will be found useful with further studies.

In accordance with the present invention, the location of the right hand motor area and relaxed motor threshold are first identified over the left hemisphere. (See e.g., Epstein CM, Lah JK, Meador K, Weissman JD, Gaitan LE, Dihenia B, Optimized stimulus parameters for lateralized suppression of speech with magnetic brain stimulation, *Neurology*, 1996; 47: 1590-1593, the disclosure of which is fully incorporated herein by reference). During stimulation at a rate of 1 Hz, the magnetic coil is moved across the left central region and the stimulator output is gradually adjusted to locate the point of lowest-intensity activation, followed by the magnetic threshold at that site. This position is then labelled with a permanent marker. Determining motor threshold requires only approximately 5-10 minutes at the first treatment session, and less time in subsequent sessions because the location has already been marked. Location of the marked area is facilitated by the use of center port 62.

The site of rTMS treatment is measured 5 cm anteriorly from the hand motor area on a parasagittal line. (See e.g., George MS, Wasserman EM, Williams W., et al., Changes in mood and hormone levels after rapid-rate transcranial magnetic stimulation of the prefrontal cortex, *J. Neuropsychiatry Clin. Neurosci.* 1996; 8:172-180, the disclosure of which is fully incorporated herein by reference.) At each rTMS treatment, the stimulator output is set to 110% of relaxed motor threshold and a repetition rate of 10 Hz. Stimulation is delivered in ten trains of 5 seconds each, with trains beginning 30 seconds apart. The coil is oriented so that electric fields are induced along a sagittal plane. Ear protection was worn throughout.

During use of the device for treatment, all treatments were administered once daily for five (5) consecutive weekdays. Patients lay supine with the head elevated on a pillow. Continuous cardiac monitoring was performed, and blood pressure was taken every 60 seconds during stimulation. rTMS was performed using a damped cosine pulse and the ferromagnetic core stimulator disclosed herein.

Using this magnetic stimulator, left prefrontal rTMS was effected with good results. The device and method were tested on 32 patients who had been referred for electroconvulsive therapy (ECT). Ten patients had previously received ECT. All patients studied had received at least one six week trial of an antidepressant at a therapeutic dose (See Table 1 of Figure 5). All of the patients met DSM-IV criteria for a Major Depressive episode (29 unipolar, 3 bipolar), were rated at least moderately ill on the Clinical Global Impression Scale (CGI) and had a pre-treatment score on the Hamilton Depression Scale (Ham-D, 21 item) greater than 20. Diagnoses were made by a physician (GSF) using a DSM-IV checklist during a structured clinical interview.

In general, patients were tapered off psychotropic medications prior to beginning a course of rTMS, although in our studies, four of the patients could not be taken off of medications due to the severity of their illness. In no case was a patient started on a new psychotropic medication during rTMS treatment. Patients with a history of recent myocardial infarction, cardiac pacemaker, intracranial metallic objects or increased intracranial pressure were excluded. Responders were characterized according to the criteria of Sackheim, et al.: they had to show a 60% reduction from their pre-treatment Ham-D score and a post-rTMS maximum score of 16 points. (See, Sackheim HA, Decina P, Portnoy S, Kanzler M, Kerr B, Malitz S., Effects of electrode placement on the efficacy of titrated low-dosage ECT, *Am. J. Psychiatry*, 1987; 144: 1449-1455, the disclosure of which is fully incorporated herein by reference.) In addition, responders had to be rated as moderately to markedly improved on a 7 point CGI. These ratings were completed by the patient's clinical treatment team along with the physician on the rTMS service (GSF). All ratings were obtained prior to beginning rTMS and within 48 hours after the fifth treatment.

Of those patients studied, 28 out of 32 completed the course of rTMS treatments. Mean Ham-D scores fell from 31 to 15 ( $p < .0001$ ). There were 16 responders (56%) and 12 non-responders (44%). Fourteen patients (50%) had post-treatment Ham-D scores of less than 10. When the differences in post-treatment and pre-treatment Ham-D scores were plotted on a histogram, the non-responders and responders appeared to fall into two distinct clusters (See Figure 6). Patients who responded to rTMS did not differ with respect to age ( $p = 0.3$ ), sex ( $p = 0.5$ ) or pre-rTMS Ham-D scores ( $p = 0.4$ ) from non-responders (See Table 2 in Figure 5). Fourteen of the 25 (56%) patients with Major Depression (Unipolar, Recurrent) responded to treatment using the present stimulator. One of the 2 patients with Psychotic Depression responded (See Table 3 in Figure

5). Two of 3 patients with Bipolar Disorder responded to rTMS using the present stimulator (See Table 3 in Figure 5). Of ten patients who reported a favorable response to ECT in the past, 8 of these responded to rTMS using the present magnetic stimulator.

Accordingly, the present device and method has been found to be useful for treatment of depression as an alternative to the devices and methods previously used in the art.

In several patients studied, however, some adverse events were reported. Two patients (a 47 year old male and a 33 year female) requested termination after one treatment because of pain over the left frontal region during stimulation. In both cases, the pain stopped immediately, when stimulation ceased.

A 44 year old female with preexisting motor tics of the right and lower extremity had recurrence of these movements during the first rTMS treatment. Periodic limb flexion persisted for 20 minutes without change in speech or alertness, and could be quenched repeatedly with gentle pressure to the arm or leg. Movements ceased after 2 mg of lorazepam IV, without any subsequent complications.

A 51 year old hypertensive female developed left arm, leg, and lower face paresthesias 20 minutes after her first rTMS treatment. Paresthesias remitted completely over several days. Complete neurological examination five hours after onset was normal. MRI and MRA the next day were normal. This event was assessed as a probable small lacunar infarction in the right hemisphere.

A 46 year old female, who was a responder to rTMS, initially reported that she had no history of epilepsy prior to beginning treatment; however, two weeks after starting treatment she reported apparent left focal motor seizures, and admitted preexisting twitching of the left face. All episodes were remote from the times of rTMS by at least several hours.

Complete neurological examination, EEG, and MRI were normal. Seizures continued and became bilateral despite therapeutic phenytoin levels, and were highly correlated with attendance at church and funerals. She underwent inpatient video-EEG monitoring, which confirmed a diagnosis of psychogenic pseudoseizures.

Ten patients complained of mild headache during treatment. These headaches ended immediately after stimulation stopped; all ten patients completed the course of rTMS, and none required treatment with analgesics. No patients complained of memory or cognitive side effects during or after rTMS. rTMS had no effect on blood pressure or heart rate.

Accordingly, the present inventions are believed to be significant improvements over the prior art, and have application in characterization, localization and treatment of brain function, including for depression and speech arrest. In addition to the disclosure of the inventions provided herein, several additional references may be of interest to those of ordinary skill and useful for additional background and information of relevance. These references include:

1. Pascual-Leone A, Gates JR, Dhuna A. Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. *Neurology* 1991;41:697-702.
2. Michelucci R, Valzania F, Passarelli D, et al. Rapid-rate transcranial magnetic stimulation and hemispheric language dominance: usefulness and safety in epilepsy. *Neurology* 1994;44:1697-1700.
3. Jenum P, Friberg L, Fuglsang-Frederiksen A, Dam M. Speech localization using repetitive transcranial magnetic stimulation. *Neurology* 1994;44:269-273.

4. Pascual-Leone A, Houser CM, Reese K, et al. Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. *Electroenceph Clin Neurophysiol* 1993;89:120-130.
5. Lesser RP, Luders H, Klem G, et al. Extraoperative cortical functional localization in patients with epilepsy. *J Clin Neurophysiol* 1987;4:27-53.
6. Ojemann GA, Sutherling WA, Lesser RP, Dinner DS, Jayakar P, Saint Hilaire J-M. Cortical stimulation. In: Engel J, Jr, ed. *Surgical treatment of the epilepsies*. 2nd ed. New York: Raven Press, 1993:399-414.
7. Cherlow DG, Dymond AM, Crandall PH, Walter RD, Serafetinides EA. Evoked response and after-discharge thresholds to electrical stimulation in temporal lobe epileptics. *Arch Neurol* 1977;34:527-531.
8. Epstein CM, Schwartzberg DG, Davey KR, Sudderth DB. Localizing the site of magnetic brain stimulation in humans. *Neurology* 1990;40:666-670.
9. Wassermann EM, McShane LM, Hallett M, Cohen LG. Noninvasive mapping of muscle representations in human motor cortex. *Electroenceph Clin Neurophysiol* 1992;85:1-8.
10. Sackeim HA, Decina P, Portnoy S, Kanzier M, Kerr B, Malitz S. Effects of electrode placement on the efficacy of titrated low-dosage ECT. *Am J Psychiatry*, 1987; 144:1449-1455
11. Pascual-Leone A, Houser CM, Reeves K, et al. Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. *Electroencephalogr Clin Neurophysiol*. 1993; 89:120-130.
12. Wasserman EM, Grafman J, Berry C, Hollnagel C, Wild K, Clark K, Hallett M. Use and safety of a new repetitive transcranial magnetic stimulator.

13. Hufnagel A, Claus D, Brunhoelzl C, Sudhop T. Short-term memory: no evidence of effect of rapid-repetitive transcranial magnetic stimulation in healthy individuals. *J Neurol.* 1993;240:373-376.
14. Fleischmann A, Prolov K, Abarbanel J, Belmaker RH. The effect of transcranial magnetic stimulation of rat brain on behavioral models of depression. *Brain Research.* 1995;699:130-132.
15. Fleischmann A, Steppel J, Leon A, et al. The effect of transcranial magnetic stimulation compared with electroconvulsive shock on rat apomorphine induced stereotypy. *Eur Neuropsychopharmacol.* 1994;4:449-450.
16. Klein E, Ben-Shachar D, Grisaru N, Belmaker RH. Effects of rTMS on brain monoamines, receptors and animal models of depression. Presented to Biological Psychiatry; May, 1997, San Diego, CA.
17. Epstein, CM, Schwartzberg DG, Davey KR, Sudderth DB, Localizing the site of magnetic brain stimulation in humans, *Neurology* 1990; 40:666-670.
18. Epstein CM, Lah JJ, Meador K, Weissman JD, Gaitain LE, Dihenia B, Optimum stimulus parameters for lateralized suppression of speech with magnetic brain stimulation, *Neurology*, 47: 1590-1593 (December 1996).

The disclosures of all references cited in the present application are to be considered fully incorporated herein by reference.

Having described this invention with regard to specific embodiments, it is to be understood that the description is not meant as a limitation since further modifications may suggest themselves to those skilled in the art and it is intended to cover such modifications as fall within the scope of the appended claims.



**Claims**

We claim:

1. A transcranial magnetic nerve stimulator, comprising:  
a magnetic core, said magnetic core being approximately hemispherical and having windings of wire around at least a portion of said magnetic core.
2. A transcranial magnetic nerve stimulator as claimed in Claim 1, wherein said hemispherical magnetic core is of a shape which approximately conforms to a portion of the surface of a human head.
3. A transcranial magnetic nerve stimulator as claimed in Claims 1-2, wherein said magnetic stimulator is provided with a port extending through said stimulator.
4. A transcranial magnetic nerve stimulator as claimed in Claim 1, wherein said core is made of a material which is ferromagnetic.
5. A transcranial magnetic nerve stimulator as claimed in Claim 1-4, wherein said hemispherical magnetic core is comprised of a plurality of adjacent cores.
6. A transcranial magnetic nerve stimulator as claimed in Claim 1-4, wherein said hemispherical magnetic core comprises four adjacent cores.
7. A transcranial magnetic nerve stimulator as claimed in Claims 1-6, wherein said magnetic core comprises a magnetic material having a magnetic saturation of at least 0.5 Tesla.

8. A transcranial magnetic nerve stimulator as claimed in Claims 1-6, wherein said magnetic core comprises a magnetic material having a magnetic saturation of at least 1.5 Tesla.
9. A transcranial magnetic nerve stimulator as claimed in Claims 1-6, wherein said magnetic core comprises a magnetic material having a magnetic saturation of at least 2.0 Tesla.
10. A transcranial magnetic nerve stimulator as claimed in Claims 1-9, wherein at least one of said adjacent cores spans an angle of approximately 208 degrees.
11. A transcranial magnetic nerve stimulator as claimed in Claims 1-9, wherein at least one of said adjacent cores spans an angle of approximately 205-215 degrees.
12. A transcranial magnetic nerve stimulator as claimed in Claim 1-9, wherein at least one of said adjacent cores spans an angle of approximately 190-230 degrees.
13. A transcranial magnetic nerve stimulator as claimed in Claims 1-9, wherein at least one of said adjacent cores spans an angle of approximately 180 - 270 degrees.
14. A transcranial magnetic nerve stimulator as claimed in Claims 1-9, wherein all of said adjacent cores span an angle of approximately 208 degrees.

15. A transcranial magnetic nerve stimulator as claimed in Claims 1-9, wherein all of said adjacent cores span an angle of approximately 205-215 degrees.

16. A transcranial magnetic nerve stimulator as claimed in Claims 1-9, wherein all of said adjacent cores span an angle of approximately 190-230 degrees.

17. A transcranial magnetic nerve stimulator as claimed in Claims 1-9, wherein all of said adjacent cores span an angle of approximately 180 - 270 degrees.

18. A transcranial magnetic nerve stimulator as claimed in Claims 1-17, further comprising a power source for providing power to said stimulator.

19. A transcranial magnetic nerve stimulator as claimed in Claims 1-18, wherein said magnetic material comprises vanadium permendur.

20. A transcranial magnetic nerve stimulator as claimed in Claims 1-18, wherein at least one of said cores comprise vanadium permendur.

21. A transcranial magnetic nerve stimulator as claimed in Claim 1-18, wherein all of said cores comprise vanadium permendur.

22. A transcranial magnetic nerve stimulator as claimed in Claims 1-21, wherein at least one of said cores comprise 3% grain oriented steel.

23. A transcranial magnetic nerve stimulator as claimed in Claims 1-21, wherein all of said cores comprise 3% grain oriented steel.

24. A transcranial magnetic nerve stimulator as claimed in Claims 1-23, wherein one of said cores comprises a 50% nickel alloy.

25. A transcranial magnetic nerve stimulator as claimed in Claims 1-24, wherein at least one of said cores has an outer diameter between approximately 2 and 7 inches.

26. A transcranial magnetic nerve stimulator as claimed in Claims 1-24, wherein all of said cores have an outer diameter between approximately 2 and 7 inches.

27. A transcranial magnetic nerve stimulator as claimed in Claims 1-26, wherein at least one of said cores has an inner diameter between approximately 0.2 and 1.5 inches.

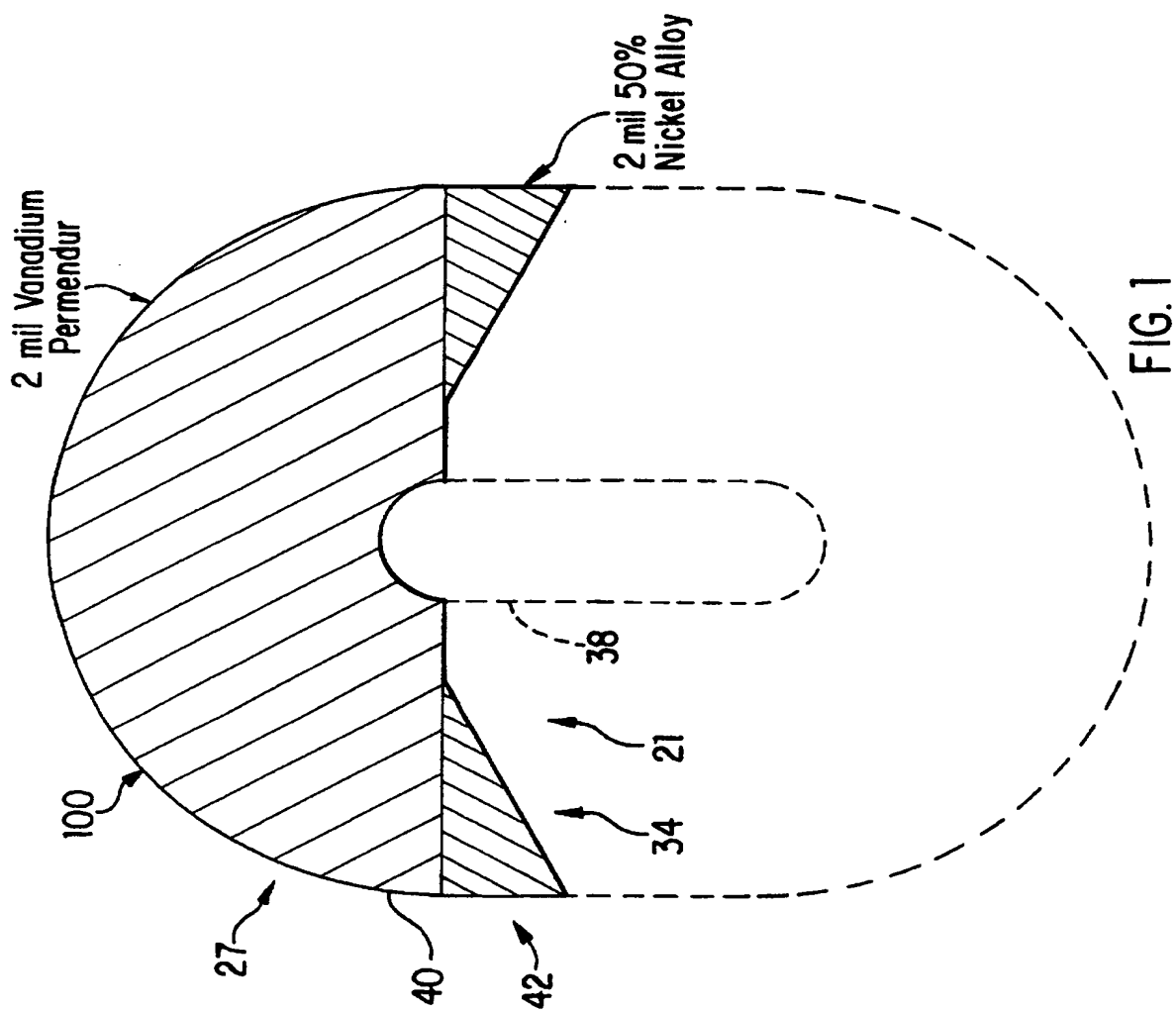
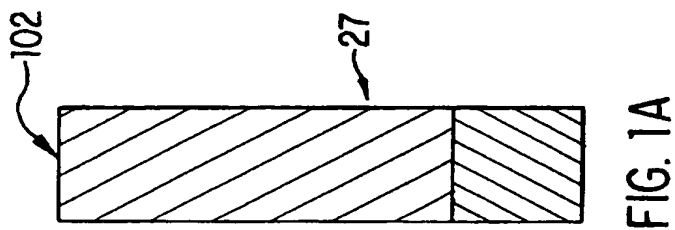
28. A transcranial magnetic nerve stimulator as claimed in Claims 1-26, wherein all of said cores have an inner diameter between 0.2 and 1.5 inches.

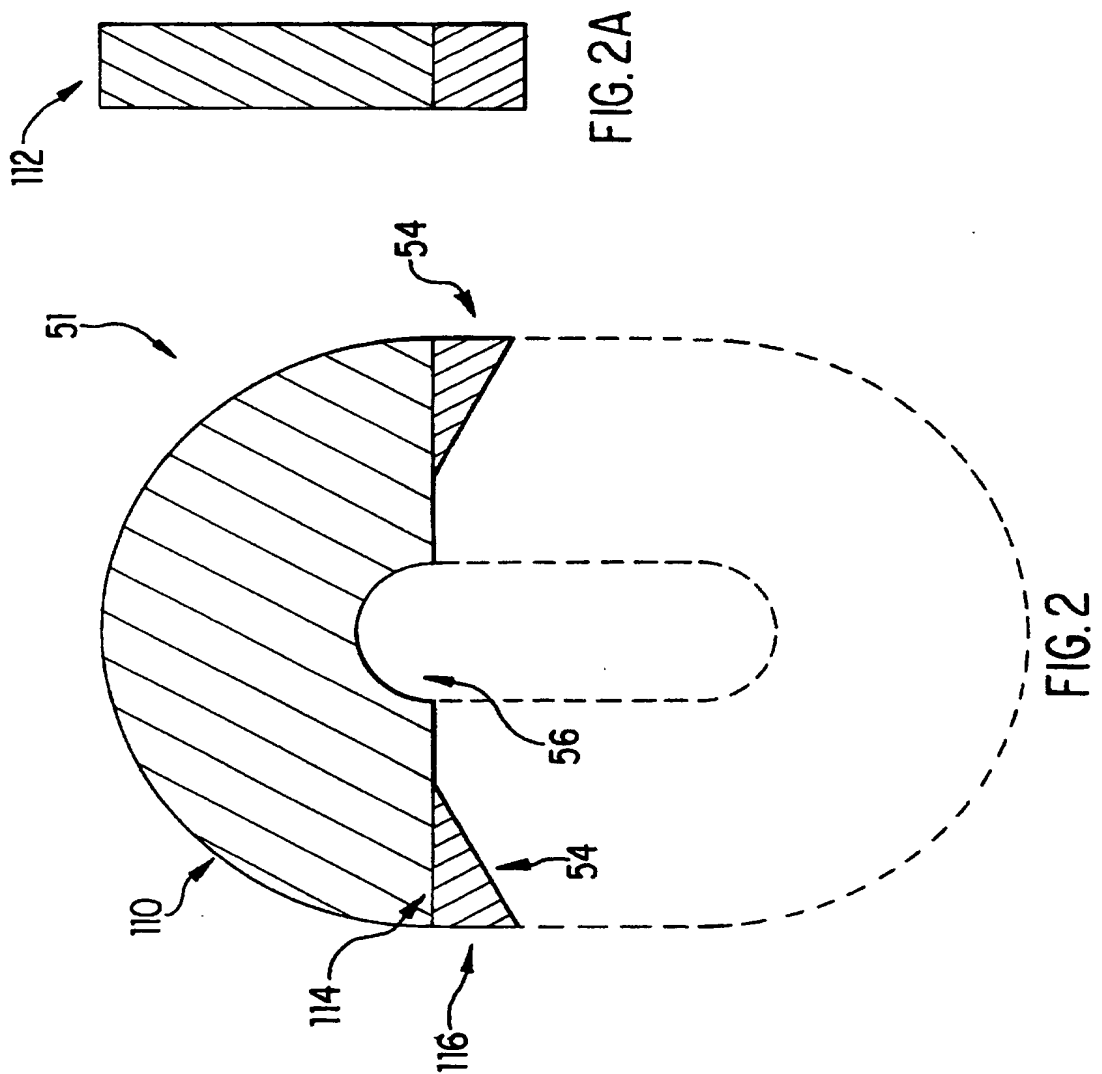
29. A transcranial magnetic nerve stimulator as claimed in Claims 1-28, wherein said core comprises a semicircular section and two triangular sections, said semicircular section and said two triangular sections being integrally formed as a single piece.

30. A transcranial magnetic nerve stimulator as claimed in Claims 1-29, wherein said core comprises a semicircular section further having two triangular sections attached thereto.

31. A transcranial magnetic nerve stimulator as claimed in Claims 1-30, wherein said core is comprised of at least two separate magnetic materials
32. A transcranial magnetic nerve stimulator as claimed in Claims 1-31, wherein one of said materials is a 50% nickel alloy
33. A transcranial magnetic nerve stimulator as claimed in Claims 1-32, wherein said materials comprise vanadium permendur and a 50% nickel alloy.
34. A method for treatment of depression, comprising  
(a) selecting a patient suffering from a depressive disorder; and,  
(b) magnetically stimulating the brain of the patient transcranially using a transcranial magnetic stimulator having a ferromagnetic core.
35. A method for treatment of depression as claimed in Claim 34, wherein said stimulator is a stimulator in accordance with Claims 1-33.
36. A method for studying the brain, comprising:  
(a) Directing a subject to perform a predetermined task; and,  
(b) Magnetically stimulating the brain of said subject transcranially during performance of said predetermined task using a transcranial magnetic stimulator having a ferromagnetic core; and,  
(c) Monitoring the speech arrest of said subject due to said magnetic stimulation.

1/8





3/8

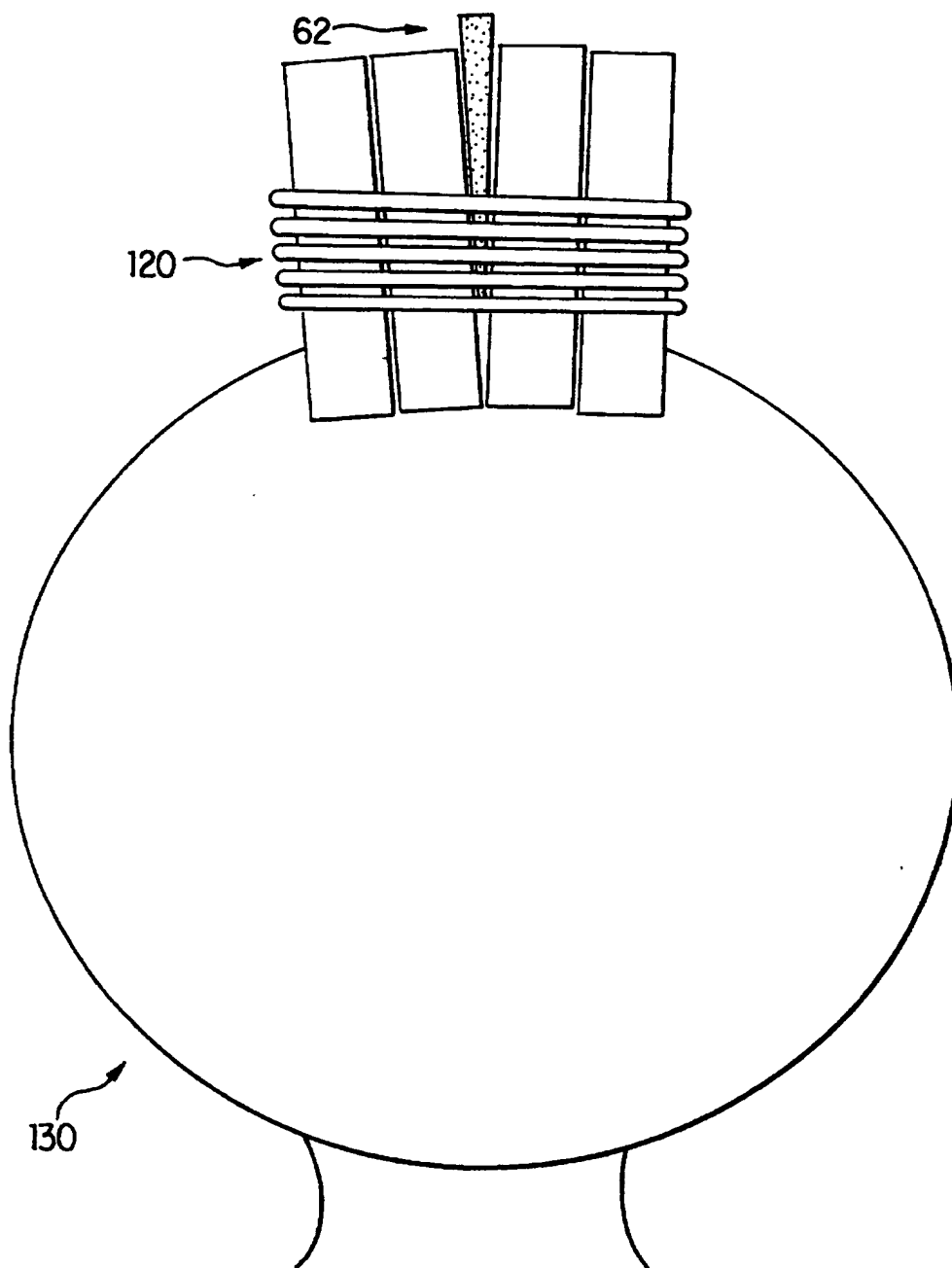


FIG. 3



4/8

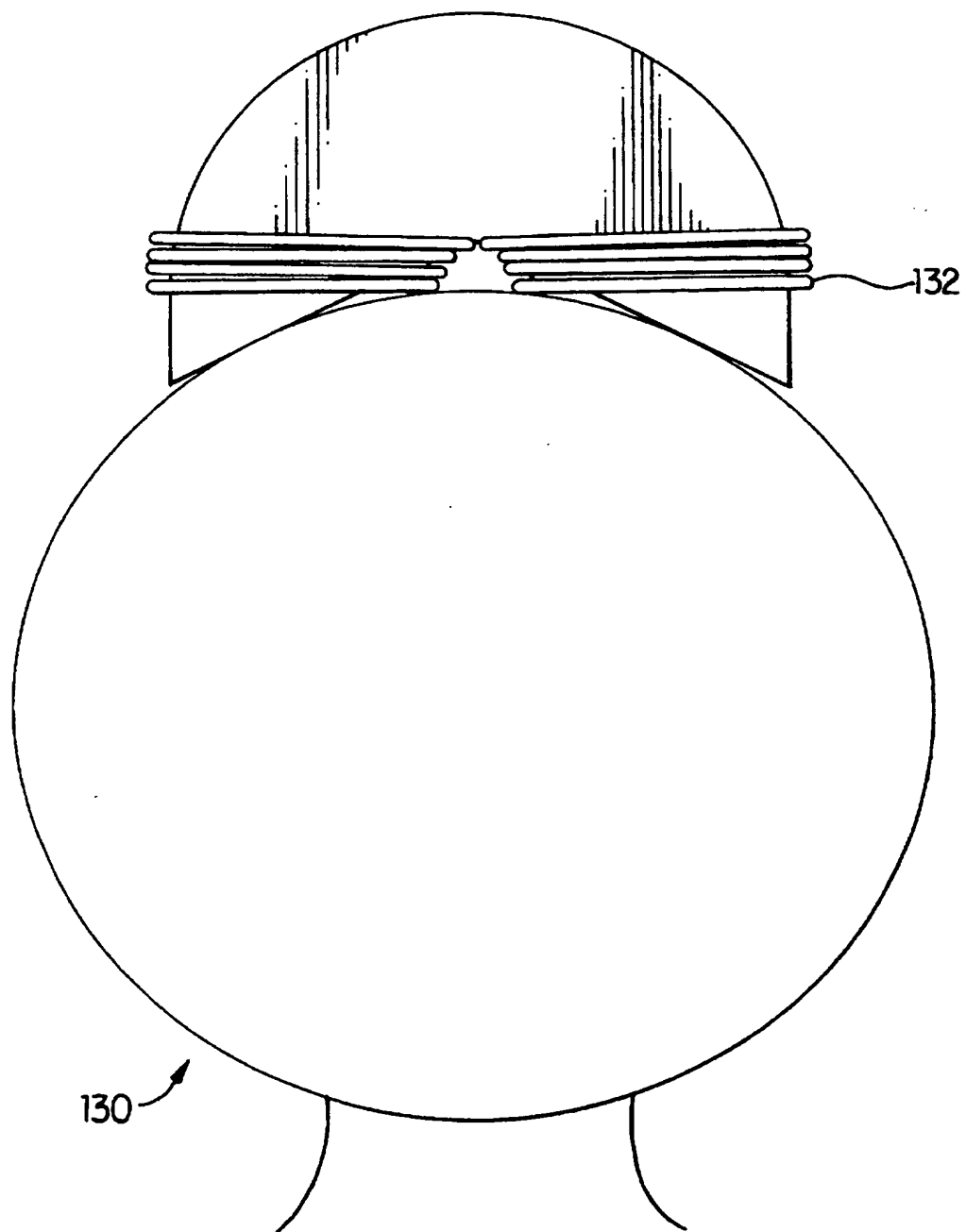


FIG. 4

5/8

TABLE: 1  
ANTIDEPRESSANT DOSAGES RECEIVED  
PRIOR TO rTMS

| MEDICATION DOSAGES       | # OF PATIENTS TAKING |
|--------------------------|----------------------|
| PAXIL $\geq$ 20 mg       | 15                   |
| PROZAC $\geq$ 20 mg      | 6                    |
| ZOLOFT $\geq$ 50 mg      | 4                    |
| TRAZADONE $\geq$ 200 mg  | 1                    |
| EFFEXOR $\geq$ 150 mg    | 1                    |
| WELLBUTRIN $\geq$ 300 mg | 3                    |

TABLE: 2  
AGE AND SEX OF RESPONDERS & NON-RESPONDERS

| AGE     | RESPONDERS | NON-RESPONDERS |
|---------|------------|----------------|
| MEAN    | 35         | 46             |
| RANGE   | 32-62      | 22-64          |
| MALES   | 7          | 7              |
| FEMALES | 9          | 5              |

TABLE: 3  
DIAGNOSIS OF RESPONDERS AN NON-RESPONDERS

| DIAGNOSIS  | RESPONDERS | NON-RESPONDERS |
|--|------------|----------------|
| MAJOR DEPRESSION<br>UNIPOLAR RECURRENT                   | 14         | 11             |
| MAJOR DEPRESSION<br>RECURRENT WITH<br>PSYCHOTIC FEATURES | 1          | 1              |
| BIPOLAR DISORDER   | 2          | 1              |

FIG.5

SUBSTITUTE SHEET (RULE 26)

6/8

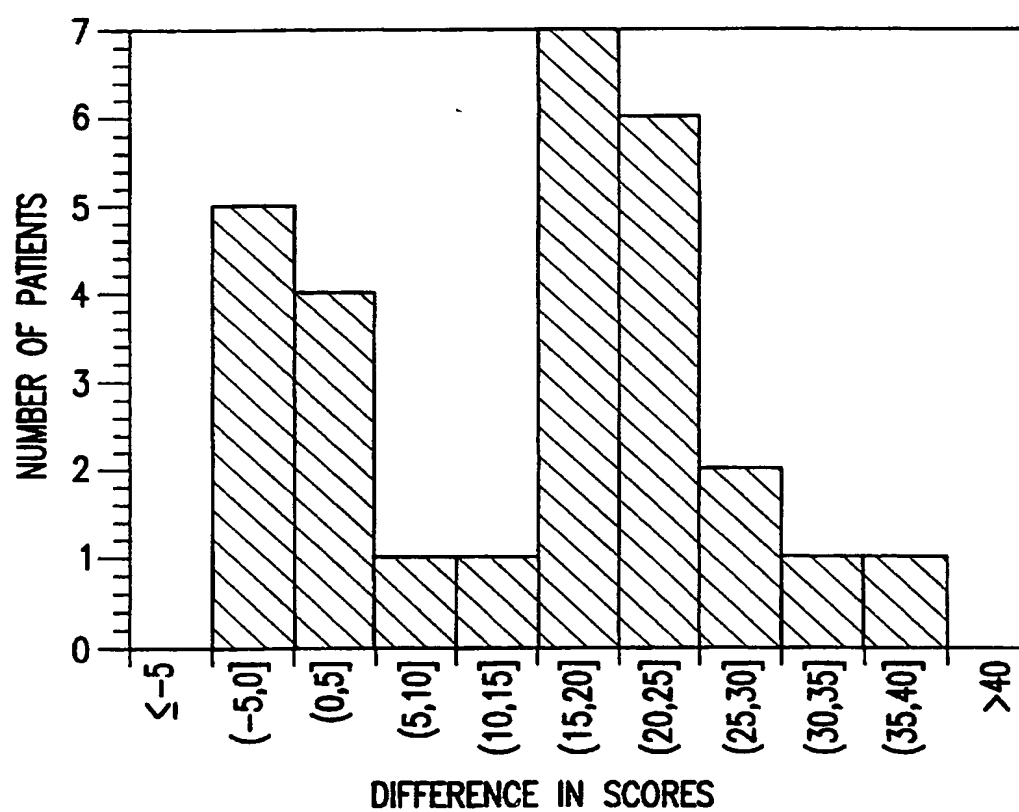


FIG.6

SUBSTITUTE SHEET (RULE 26)

7/8

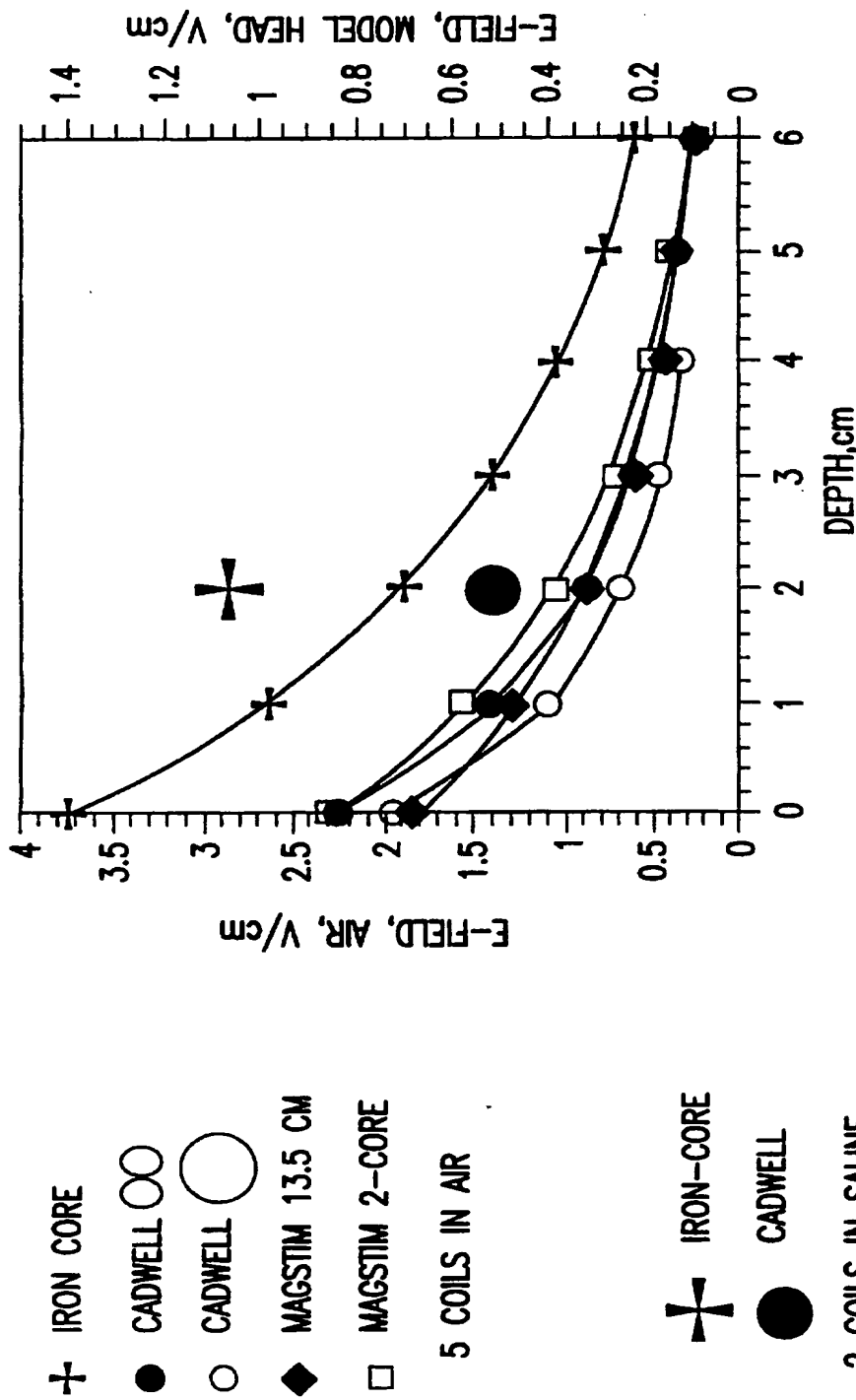


FIG.7

8/8

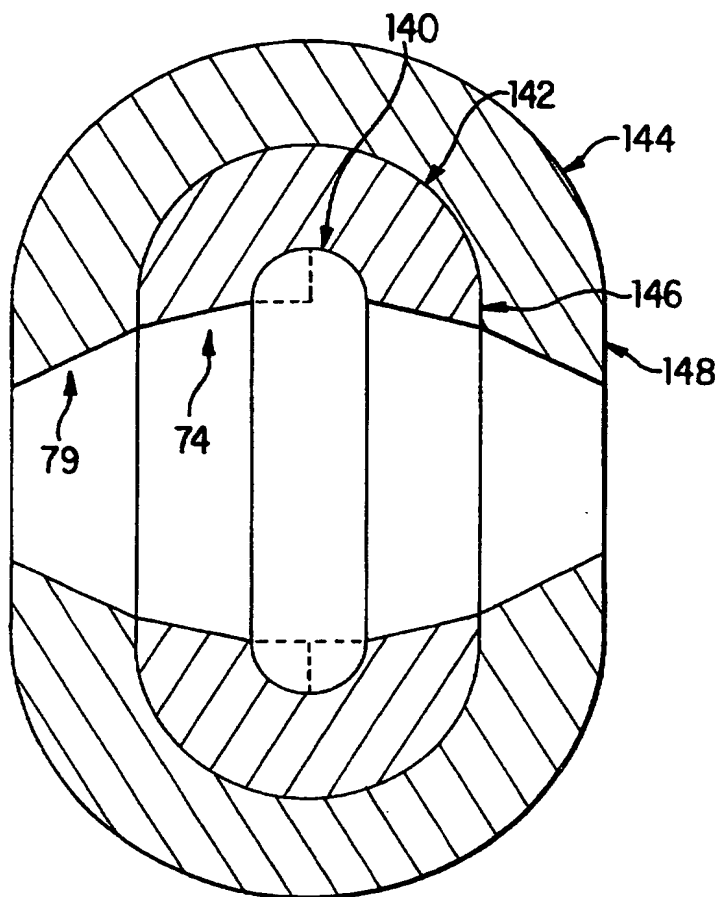


FIG. 8

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/14826

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61B 17/52; A61N 2/00

US CL : 600/009

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 600/009-015

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
NONE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X         | RU 2008946 A (MEDIPAK INNOVATION CO) 15 March 1994, Abstract.                      | 1, 2, 4               |
| A         | US 5,441,495 A (LIBOFF ET AL.) 15 August 1995, entire document.                    | 1, 2, 4, 34, 36       |
| A         | US 5,116,304 A (CADWELL) 26 May 1992, entire document.                             | 1, 2, 4, 34, 36       |
| A         | US 4,940,453 A (CADWELL) 10 July 1990, entire document.                            | 1, 2, 4, 34, 36       |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

|   |  |
|---|--|
| * Special categories of cited documents:  | *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  |
| *A* document defining the general state of the art which is not considered to be of particular relevance  | *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone   |
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Date of the actual completion of the international search

22 OCTOBER 1997

Date of mailing of the international search report

17 NOV 1997

Name and mailing address of the ISA/US  
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/14826

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 3, 5-33, 35  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

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